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Reduced renin activity in essential hypertension: A reappraisal

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Reduced renin activity in essential hypertension: A reappraisal. The apparent suppression of plasma renin activity in essential hypertensive patients compared to normotensive controls prompted an examination of factors which might be responsible for this difference in people taken from a blood pressure screening survey. Plasma renin activity was lower in 89 previously untreated "hypertensive" subjects than in an equal number of age- and sex-matched "controls" from the same community. The rise in plasma renin activity on standing or after frusemide was proportional to the resting level, and it was generally less in hypertensives, but small or absent responses were also seen in those with normal blood pressure. There was no evidence for a "low renin subgroup" among the hypertensives. Plasma renin activity fell with both increasing age and increasing arterial pressure. A low renin activity is more likely to be a consequence of hypertension than to be associated with its cause.

Diminution de l'activité rénine au cours de l'hypertension artérielle: Une ré-évaluation. La suppression apparente de l'activité rénine plasmatique chez les malades atteints d'hypertension essentielle par comparaison avec des témoins à pression artérielle normale a suscité l'étude des facteurs qui peuvent être responsables de cette différence chez des sujets appartenant à une enquête sur l'hypertension artérielle. L'activité rénine plasmatique était plus faible chez 89 sujets atteints d'hypertension non traitée antérieurement que chez un nombre égal de sujets témoins d'âge et de sexe correspondants, appartenant à la même communauté. L'augmentation de l'activité rénine plasmatique en position debout ou après furosémide est proportionnelle au niveau de base, elle est généralement inférieure chez les sujets atteints d'hypertension, mais des réponses nulles ou faibles ont aussi été observées chez des sujets ayant une pression artérielle normale. Il n'y a pas eu de preuve de l'existence d'un sous-groupe "à activité rénine basse" parmi les malades atteints d'hypertension artérielle. L'activité rénine plasmatique diminue à la fois en fonction de l'âge et de l'augmentation de la pression artérielle. Une activité rénine faible est plus probablement une conséquence de l'hypertension qu'un fait associé à sa cause.

A substantial proportion of patients with benign essential hypertension show a reduction in plasma renin activity (PRA), whether this is measured at rest or in response to stimuli such as standing, sodium depletion, or diuretic treatment [1–4]. Renin activity tends to decrease with age in hypertensive patients, but whether it does so or not in the normotensive population is controversial [5–11]. There is also evidence of an inverse relationship between plasma renin and arterial pressure [5, 9, 12–15]. Thus, when plasma renin activity is low in a hypertensive subject, the possible effects of age, blood pressure, and, perhaps, the duration of hypertension ought to be taken into account before other causes of low renin activity are postulated. Theoretical mechanisms by which raised arterial pressures may reduce renin have been put forward [16–18]. Earlier suggestions that renin may be "suppressed" by over-secretion of an unknown mineralocorticoid do not now find general acceptance, although some investigators continue to support the hypothesis [19]. Many factors affect renin release, and interpretation of published data has been complicated by the possible effects of previous drug treatment on renin responses, by the lack of suitable control data, and by the use of differing methods for renin assay [20].

In this paper, the effects on plasma renin activity of two different stimuli to renin release, standing and frusemide, have been carefully assessed in relation to data from an equal number of hypertensive patients and of age- and sex-matched controls drawn from the same community.

Methods

Subjects with raised arterial pressure were sought from among the staff of the Atomic Energy Research

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Establishment at Harwell and from the populations of two nearby general practices. Blood pressures were measured on the first occasion by the random-zero sphygmomanometer and subsequently by the London School of Hygiene sphygomomanometer. Eighty-nine subjects whose diastolic pressures (phase 5) exceeded 100 mm Hg on each of four occasions were arbitrarily designated to have hypertension, and each was matched by a control subject, from the same community, with a diastolic pressure below 90 mm Hg (Table 1). All subjects were Caucasian. The duration of hypertension was unknown, as the patients were unaware that their blood pressures were raised until the time of screening. The blood pressure measurements used in the analyses were those taken after the subject had been lying supine for five minutes, on his fourth visit to the medical center. None of the 178 subjects had ever received antihypertensive treatment, and no other drugs were being taken. Cushings syndrome, pheochromocytoma, primary aldosteronism, and coarctation of the aorta were excluded on clinical and biochemical evidence. Subjects with retinal hemorrhages, cotton-wool spots or papilloedema, proteinuria, or an abnormal rapid-sequence excretory urogram, were excluded from the study. Also excluded were pregnant women or those taking any contraceptive pill and patients who had suffered a stroke or myocardial infarct. Endogenous creatinine clearances exceeded 75 ml/min in all 178 subjects. All gave informed consent to the procedures entailed in this study.

Plasma renin activity was measured by the method of Sealey and Laragh [21]. Blood samples for renin activity were taken at 11 00 hr after two hours of resting supine, at 13 00 hr after two hours of being erect, and at 14 00 hr one hour after i.v. administration of frusemide (1 mg/kg of body wt). Urinary sodium excretion was measured during the 24 hr immediately preceding the blood sampling. All subjects were investigated as out-patients, and they continued on their normal home diets (salt intake was not controlled).

Differences between groups were assessed by Student's unpaired t test, and where the distributions were skewed, the logarithmic values were used. The relations between variables were measured by Pearson's correlation and partial correlation tests. Differences between regression lines were assessed using t tests. The distributions were assessed by measurement of kurtosis (peakedness) and of skewness. The results are expressed as the mean value ± SEM.

Table 1. Characteristics of the people studied

	Hypertensives	Controls	P
Number	89	89	
Male : female	71:18	71:18	
Age range, *yr*	30 to 67	30 to 67	
mean	52.2	51.8	
Systolic BP, *mm Hg*	161.5 ± 2.1	123.0 ± 1.3	<0.001
Diastolic BP, *mm Hg*	104.2 ± 0.9	78.0 ± 1.4	<0.001

Table 2. Plasma renin activity (PRA) and renin responsiveness in essential hypertensive and matched control subjects

Stimuli	PRA, *ng/ml/hr*		P
	Hypertensives	Controls	
Supine	1.29 ± 0.06	1.45 ± 0.09	NS
Erect	2.70 ± 0.20	3.55 ± 0.21	<0.005
After frusemide i.v.	3.87 ± 0.31	6.29 ± 0.40	<0.001
ΔS-E[a]	1.40 ± 0.18	2.12 ± 0.17	<0.005
ΔS-L[b]	2.55 ± 0.28	4.90 ± 0.35	<0.001
ΔE-L[c]	1.22 ± 0.17	2.74 ± 0.25	<0.001

[a] ΔS-E is the change in PRA from supine to erect.
[b] ΔS-L is the change from supine to post-frusemide.
[c] ΔE-L is the change from erect to post-frusemide.

Results

In Table 2, plasma renin activities (PRA) in the hypertensive patients are compared with those of the control subjects. Average supine values were lower in the hypertensive group, although not significantly so ($P < 0.06$). After standing or injection of frusemide, renin activity increased in both groups, but the response was significantly less in the hypertensive group (Table 2). Sodium excretion over 24 hr was similar in the hypertensives (150.79 ± 5.62 mmoles) and matched controls (157.91 ± 4.99), and in neither group was there any correlation between plasma renin activity and 24-hr sodium excretion. The hypertensive subjects were slightly heavier (77.26 ± 1.11 kg) than the control subjects (72.11 ± 1.08 kg).

Figure 1 shows the frequency distributions of renin activity in the hypertensive and control subjects. There was no evidence of a bimodal distribution in either group, whether the samples were taken from supine, erect, or frusemide-treated subjects. After logarithmic transformation, to separate the crowded lower renin values in an attempt to reveal a subpopulation, these distributions were shown statistically to be not different from a normal distribution.

The rise of renin after either stimulus was related to the prevailing renin activity (Fig. 2). Poor responses were not confined to those with the lowest supine values but occurred throughout the range of supine PRA, nor were sluggish responses confined to the hypertensive group (Fig. 2).

An inverse correlation between age and plasma renin activity was confirmed for both hypertensive and control subjects (Table 3). Blood pressure and

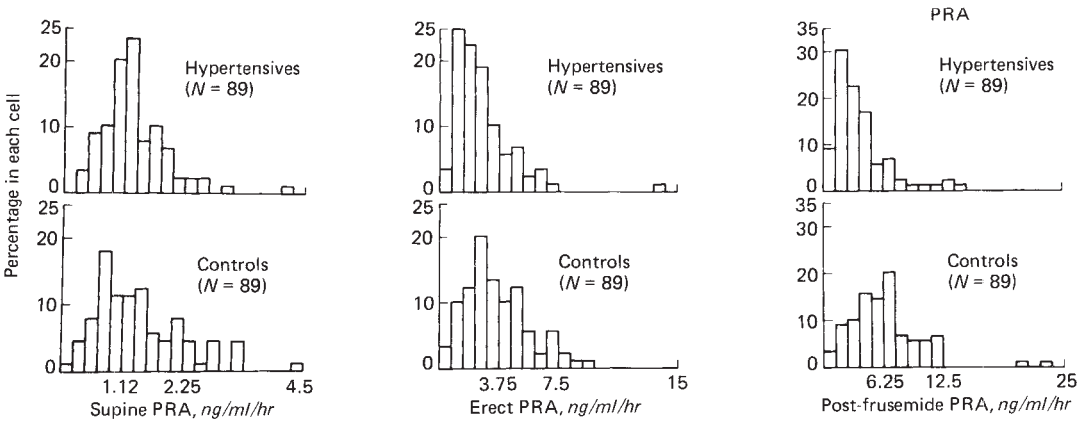

Fig. 1. *Frequency distributions of plasma renin activity (PRA) in essential hypertensive and matched control subjects.*

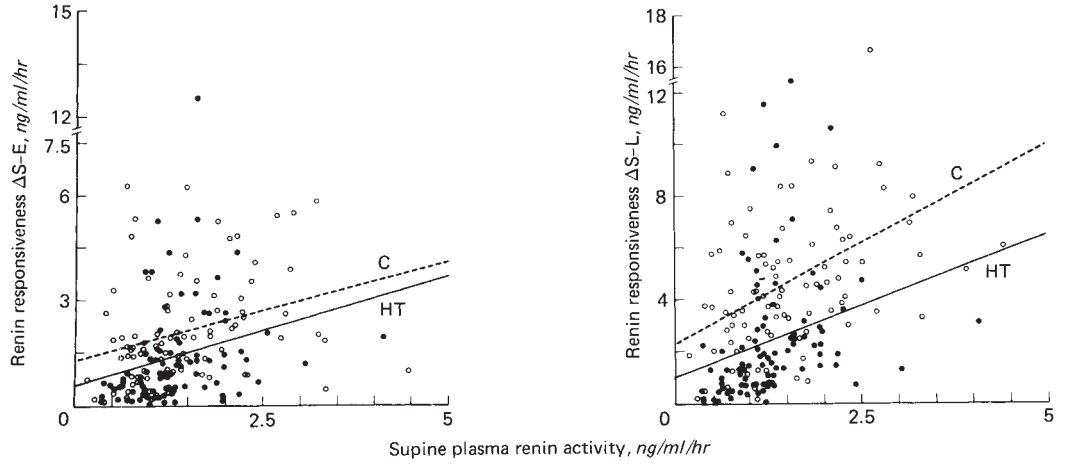

Fig. 2. *The relationship between supine plasma renin activity (PRA) and renin responsiveness.* ΔS-E is the change in PRA from supine to erect, and ΔS-L is the change in PRA from supine to post-frusemide. *Closed circles* (•) represent hypertensive, and open circles (○), control subjects. The *continuous* (hypertensive, HT) and the *dotted* (control, C) *regression lines* illustrate the relationship between ΔS-E response and supine PRA (hypertensive $r = 0.24$, $P < 0.03$; controls $r = 0.30$, $P < 0.004$) and between Δ S-L and supine PRA (hypertensives $r = 0.27$, $P < 0.02$; controls $r = 0.46$, $P - 0.001$). The difference between the regression lines was not significant.

Table 3. Correlations of renin and its responsiveness with age and blood pressure

	Plasma renin activity			Renin responsiveness[a]		
	Supine	Erect	After i.v. frusemide	ΔS-E	ΔS-L	ΔE-L
Age						
hypertensives	−0.19	−0.44[d]	−0.48[d]	−0.44[d]	−0.48[d]	−0.35[d]
controls	−0.27[b]	−0.40[d]	−0.44[d]	−0.37[d]	−0.43[d]	−0.37[d]
Systolic BP						
hypertensives	−0.15	−0.23[b]	−0.30[c]	−0.21[b]	−0.29[c]	−0.26[b]
controls	−0.14	−0.21[b]	−0.23[b]	−0.19	−0.22[b]	−0.20
Diastolic BP						
hypertensives	−0.01	−0.23[b]	−0.30[c]	−0.27[c]	−0.32[c]	−0.24[b]
controls	−0.08	−0.15	−0.23[b]	−0.15	−0.23[b]	−0.24[b]

[a] ΔS-E is the change in PRA from supine to erect, ΔS-L from supine to post-frusemide, and ΔE-L from erect to post-frusemide.
[b] $P < 0.05$.
[c] $P < 0.01$.
[d] $P < 0.001$.

Table 4. Partial correlations of renin and its responsiveness with age and blood pressure

Correlation to be corrected	Corrected for the effect of	Plasma renin activity			Renin responsiveness[a]		
		Supine	Erect	After i.v. frusemide	ΔS-E	ΔS-L	ΔE-L
Systolic BP	Age						
hypertensives		−0.19	−0.44[d]	−0.49[d]	−0.44[d]	−0.48[d]	−0.35[d]
controls		−0.25[b]	−0.39[d]	−0.41[d]	−0.37[d]	−0.40[d]	−0.32[c]
Diastolic BP	Age						
hypertensives		−0.20	−0.45[d]	−0.50[d]	−0.45[d]	−0.49[d]	−0.35[d]
controls		−0.27[b]	−0.42[d]	−0.43[d]	−0.38[d]	−0.42[d]	−0.33[c]
Age	Systolic BP						
hypertensives		−0.14	−0.23[b]	−0.30[c]	−0.20	−0.29[c]	−0.25[b]
controls		−0.06	−0.09	−0.11	−0.08	−0.10	−0.10
Age	Diastolic BP						
hypertensives		−0.01	−0.25[b]	−0.32[c]	−0.28[c]	−0.34[d]	−0.24[b]
controls		−0.03	−0.08	−0.17	−0.08	−0.17	−0.19

[a] ΔS-E is the change in PRA from supine to erect, ΔS-L from supine to post-frusemide, and ΔE-L from erect to post-frusemide.
[b] $P < 0.05$.
[c] $P < 0.01$.
[d] $P < 0.001$.

renin activity were also inversely correlated, but more consistently in hypertensives than in controls (Table 3). A partial correlation analysis showed age and blood pressure to exert independent effects on plasma renin activity in hypertensive patients, but in control subjects the correlations between renin and blood pressure were lost when correcting for the effects of age (Table 4).

Discussion

The investigation of previously untreated hypertensive patients, each age- and sex-matched with a control subject from the same community, allows the firm conclusion that renin activity is reduced in patients with hypertension, independent of the effects of aging and of previous drug therapy. The patients in this study had a mild form of hypertension, and, therefore, the results may not be relevant to individuals with sustained, markedly elevated blood pressure readings. Until now, the known tendency of blood pressure to increase with age has left open the possibility that aging might be an important factor in previously described inverse relationships between blood pressure and renin activity [5, 9, 12–15]. The presence of the matched control group in this series permits a more critical assessment of the relationship between arterial pressure and renin; when the effects of age are allowed for the inverse correlation between blood pressure and renin remains significant in the hypertensive subjects.

The separation of some hypertensive patients into a "low renin group" is difficult to make on sound statistical grounds. Much of the conflicting data in this field can be accounted for by the lack of a universally accepted definition of what constitutes low-renin hypertension. The two criteria most frequently used in defining this condition are the absolute renin levels and the responsiveness to a renin-elevating stimulus. It has been shown that the distribution of plasma renin [8] and angiotensin II [22] form part of a continuum with no evidence of bimodality. Any attempt to subdivide these distributions must be completely arbitrary, and the data available from this study does not suggest that such a separation is reasonable. The low-salt diet has become the "standard" stimulus to renin release [20]. More rapid, yet reliable, replacement stimuli have been sought as possible out-patient tests of renin responsiveness, and in this regard, frusemide has been extensively used both orally [23–27] and i.v. [1–3, 28]. The results are conflicting as to the value of frusemide in "separating" a low-renin subgroup of essential hypertension. Nevertheless, Kaplan et al have shown recently that frusemide, given i.v., identifies the same group of patients whose renin levels respond poorly to a low-salt diet [29], and we have confirmed this work by showing excellent correlations between the renin response to i.v. frusemide and a low-salt diet (to be published). The pattern of change of renin activity between supine and stimulated measurements is qualitatively similar, even if quantitatively different, between hypertensives and controls (Fig. 2). In both groups the degree of rise in renin activity is dependent on the supine level; the highest rises are seen in those with the highest supine levels and vice versa. The essential difference between the two groups lies in the lesser degree of rise in the hypertensive group, a characteristic trend which is found throughout the range of supine values and not confined to those with the lowest supine

levels (Fig. 2). This observation suggests that a tendency for renin responsiveness to be depressed is a characteristic of many hypertensive patients, but this tendency is not a feature of any subgroup which can be statistically separated.

It is important to note that a considerable variation in renin responses can be observed for subjects whose arterial pressures are normal as well as for the hypertensive patients. Physiologic differences must exist between patients of the same age, sex, and blood pressure, in some of whom renin rises markedly after stimulation but fails to do so in others. Whether this is a question of differences in duration of hypertension or of the distribution and severity of changes in the renal circulation is not apparent. The effect of hypertension itself on renin activity provides at least a partial explanation of lower renin activity in hypertension without the need to invoke the presence of excessive secretion of an unknown mineralocorticoid. Possible mechanisms by which raised arterial pressure and aging might reduce the capacity of the kidney to increase plasma renin activity have been discussed by others [5–10, 16–18]. Their concepts are difficult to prove or disprove, but this is less important than the need to establish whether or not "low renin hypertension" is an entity reflecting a *cause* of hypertension different from that of other patients. The evidence of this study and that of others [2, 30, 31] does not support the possibility of a separate cause.

Our findings and interpretation of them are not incompatible with observations that the blood pressure of patients with low renin activity responds better to diuretic agents [32] while beta-adrenergic blockade is more effective in those with high renin activity [33]. Such observations are themselves controversial but, if true, do not necessarily imply that the *etiology* of hypertension is different between the two groups: it may be, rather, that the effects of the disease on the renal circulation are different.

The failure to find any relation between urine sodium excretion and plasma renin activity is in contrast to the finding of Brunner et al [34]. In our study, the salt intake was unrestricted and moderate, as reflected by 95% of the subjects excreting between 140 and 165 mmoles of sodium in their urines, with only a single measurement of renin activity vs. urinary sodium representing each subject. In the study of Brunner et al, observations were made on the same subjects while taking low- and high-salt intakes separately, as well as when on a free diet. The relationships between renin activity and dietary sodium intake may differ, depending upon whether sodium intake has been changed acutely or reflects a more stable dietary habit. Most of the points relating the two variables in our study fell in the middle range of sodium excretion, occupying, therefore, only a part of the area described by the nomogram of Brunner et al.

It seems likely from the results of this investigation that a relatively inactive renin-angiotensin system is part of the natural history of essential hypertension. No support has been found for a separate specific entity of "low renin hypertension."

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